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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,951	04/20/2006	Brian Anderton	0380-P03923US0	8723

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DANN, DORFMAN, HERRELL & SKILLMAN
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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

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11/22/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,951	ANDERTON ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,26,27,31-36,38-46 and 53-55* is/are pending in the application.

4a) Of the above claim(s) *31,33-35,40,43-46,53 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,26,27,32,36,38,39,41,42 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/8/10 has been entered.

[2] Claims 22, 26-27, 31-36, 38-46, and 53-55 are pending in the application.

[3] Applicant's amendment to the claims, filed on 2/8/10, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's remarks filed on 2/8/10 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Rejections previously applied to claim 23 are withdrawn solely in view of the instant amendment to cancel this claim.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[6] Claims 31, 33-35, 40, 43-46, and 53-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no

allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/10/08.

[7] Claims 22, 26-27, 32, 36, 38-39, 41-42, and 55 are being examined on the merits.

Claim Objections

[8] The objections to claim 22 are withdrawn in view of the instant claim amendment.

[9] The objection to claim 55 as not ending with a period is withdrawn in view of the instant claim amendment.

[10] The objection to claim 55 as not reciting a conjunction before the last species of phosphorylation sites is maintained and in order to improve claim form, it is suggested that the claim be amended to insert “and” prior to “S435”.

Claim Rejections - 35 USC § 112, Second Paragraph

[11] The rejection of claims 22, 26-27, 32, 36, 38-39, and 41-42 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the instant claim amendment to require the tau protein or tau variant to have the recited phosphorylation sites, *i.e.,* S46, T50, S113, etc.

Claim Rejections - 35 USC § 112, First Paragraph

[12] The written description and scope of enablement rejections of claims 22, 26-27, 32, 36, 38-39, 41-42, and 55 under 35 U.S.C. 112, first paragraph, are withdrawn in

view of the instant amendment to claim 22, particularly with respect to the recited characteristics of tau protein or tau variant in part ii) and the recited characteristics of CK1 or CK1 variant in part iii).

Claim Rejections - 35 USC § 103

[13] The rejection of claims 22, 26, 32, 36, 38-39, and 55 under 35 U.S.C. 103(a) as being unpatentable over the combination of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret in view of Graves, Vitek, Hasegawa, Curran, Hanger, Morishima-Kawashima, and Anderton and the rejection of claims 41-42 further in view of Zhu are withdrawn, not in view of applicant's arguments, but solely in favor of the new rejection under 35 U.S.C. 103(a) set forth below.

[14] Claims 22, 26, 32, 36, 38-39, and 55 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Anderton et al. (US Patent 5,994,084; reference B of Form PTO-892 mailed on 10/3/08; hereafter "Anderton") in view of Singh et al. (*Mol. Cell. Biochem.* 131:181-189, 1994; hereafter "Singh1"), Singh et al. (*Mol. Cell. Biochem.* 154:143-151, 1996; document C8 of the IDS filed on 4/20/06; hereafter "Singh2"), Graves (*J. Biol. Chem.* 268:6394-6401, 1993; reference W of Form PTO-892 mailed on 10/3/08hereafter "Graves"), Vitek et al. (US Patent 6,593,512; reference A of Form PTO-892 mailed on 10/3/08; hereafter "Vitek"), and Litersky et al. (*Biochem. J.* 316:655-660, 1996; hereafter "Litersky").

The reference of Anderton teaches a model of Alzheimer's disease, the model being disclosed as a cell recombinantly expressing tau protein and a kinase that modulates the phosphorylation of the tau protein (column 2, lines 39-61). Anderton acknowledges that a combination of kinases can be used in the method (see claim 4). Anderton teaches cell-based models can be used in screening assays that involve immunoassays (column 7, lines 22-24). According to Anderton, antibodies, including monoclonal antibodies, may be produced against phosphorylated and non-phosphorylated tau epitopes (column 7, lines 24-26). Anderton teaches screening may be carried out by incubating the cell with a potential therapeutic agent and then incubating the cells with tau-specific and hyperphosphorylated tau-specific antibodies and the extent of binding of the antibodies indicates the extent to which hyperphosphorylation has occurred (column 7, lines 39-46).

The reference of Anderton does not teach or suggest using a combination of Casein Kinase 1 (CK1) *and* calcium/calmodulin-dependent protein kinase II (CaM kinase II) as a tau-phosphorylating kinase; does not teach or suggest the CK1 of SEQ ID NO:1; does not teach or suggest the tau of SEQ ID NO:2; and does not teach or suggest detecting phosphorylation of S416 of tau.

Regarding a combination of CK1 and CaM kinase II as a tau-phosphorylating kinase, Singh1 teaches that CK1 phosphorylates tau (p. 183, Table 1). Singh1 goes on to teach the possibility of two kinases together phosphorylating tau to higher stoichiometries relative to the single kinase (p. 185, column 1). According to Singh1, when tau is phosphorylated by CK1, the addition of CaM kinase II (and vice versa)

resulted in additional, rapid phosphorylation of tau (p. 185, column 1 and Figure 3; sentence bridging columns 1-2 and Figure 4). Singh2 teaches that tau can be converted to an Alzheimer-like state after phosphorylation by CK1 (p. 149, column 2, bottom), the CK1 phosphorylation sites on tau are some of the same sites found in paired helical filament tau (PHF-tau) (p. 149, column 1, bottom), and the sites of CK1 phosphorylation in PHF-tau were phosphorylated more rapidly and to a greater extent if tau is prephosphorylated by CaM kinase II (p. 143, abstract).

Regarding CK1 of SEQ ID NO:1, the reference of Graves teaches cloning of a nucleic acid encoding a CK1 polypeptide (p. 6395-6396) that has a nucleotide sequence (p. 6397) that encodes a polypeptide that is 100% identical to SEQ ID NO:1 herein (see Appendix A sequence alignment of the Office action mailed on 10/3/08).

Regarding tau of SEQ ID NO:2, Vitek teaches cloning of a nucleic acid encoding a tau polypeptide (Example 7, beginning at column 12) that has a nucleotide sequence (SEQ ID NO:7) that encodes a polypeptide that is 100% identical to SEQ ID NO:1 herein (see Appendix B sequence alignment of the Office action mailed on 10/3/08).

Regarding detecting phosphorylation of S416 of tau, Litersky teaches tau is phosphorylated at S416 by CaM kinase II (p. 659, column 2, top). Also, with respect to claim 36, Litersky teaches tau is also phosphorylated by CaM kinase II at S262 and S356.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Anderton, Singh1, Singh2, Graves, Vitek, and Litersky to practice the method of Anderton using a combination of CK1 and CaM

kinase II by detecting phosphorylation of at least S262, S356, and S416 of tau. Although the prior art does not appear to expressly teach S416 phosphorylation of tau by CK1, by determining whether a candidate substance inhibits phosphorylation of S416 of tau in the presence of a *combination* of CaM kinase II and CK1, one would have practiced determining whether and optionally the extent to which a candidate substance inhibits phosphorylation of tau at S416. One would have been motivated to use a *combination* of CK1 and CaM kinase II in the method of Anderton because Singh1 and Singh2 teaches a combination of CK1 and CaM kinase II achieves greater phosphorylation of Tau than either kinase alone. One would have been motivated to detect phosphorylation of S262, S356, and S416 in the screening method of Anderton because these are residues that are specifically phosphorylated by CaM kinase II as acknowledged by Litersky. One would have had a reasonable expectation of success to combine the teachings of Anderton, Singh1, Singh2, Graves, Vitek, and Litersky to practice the method of Anderton using a combination of CK1 and CaM kinase II by detecting phosphorylation of at least S262, S356, and S416 of tau because of the results of Anderton, Singh1, Singh2, Graves, Vitek, and Litersky. Therefore, the method of claims 22, 26, 32, 36, 38-39, and 55 would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO REMARKS: To the extent applicant's remarks address the newly applied rejection, the remarks are addressed below. Beginning at p. 13 of the instant remarks, applicant argues a *prima facie* case of obviousness has not been

established because amended claim 22 specifically identifies a select number of tau phosphorylation sites rather than any tau phosphorylation site(s), which sites were previously unknown.

Applicant's argument is not found persuasive. As noted above, S416 of tau was known to be phosphorylated by at least CaM kinase II. The prior art of record does not appear to explicitly point to S416 as a site of tau phosphorylation by CK1. However, *a priori* knowledge of whether or not CK1 phosphorylates S416 is not required. The combination of references motivates one to use a *combination* of CK1 and CaM kinase II in the method of Anderton and, contrary to applicant's position, determine whether S416 is or is not phosphorylated in the presence of CK1 and a candidate substance. In so doing, one would have practiced the step of determining whether the candidate substance inhibits S416 phosphorylation of tau.

[15] Claims 22, 26-27, 32, 36, 38-39, and 55 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Anderton in view of Lau et al. (*Current Topics Med. Chem.* 2:395-415, 2002; reference V of Form PTO-892 mailed on 10/3/08; hereafter "Lau"), Graves, Vitek, Hasegawa (*J. Biol. Chem.* 267:17047-17054, 1992; reference V of Form PTO-892 mailed on 5/12/09; hereafter "Hasegawa") and Yamamoto et al. (*Arch. Biochem. Biophys.* 408:255-262, 2002; hereafter "Yamamoto").

The teachings of Anderton are set forth above.

The reference of Anderton does not teach or suggest CK1 as a tau-phosphorylating kinase; does not teach or suggest the CK1 of SEQ ID NO:1; does not

teach or suggest the tau of SEQ ID NO:2; and does not teach or suggest determining the phosphorylation state of a full-length purified tau by mass spectrometry.

Regarding CK1 as a tau phosphorylating kinase, the reference of Lau teaches CK1 can phosphorylate tau, is tightly associated with paired helical filaments purified from Alzheimer's disease brains, three CK1 isoforms are upregulated in Alzheimer's disease brain, and that CK1 may be linked to tau pathology in Alzheimer's disease (p. 401, column 2, top). Lau further teaches "Since tau hyperphosphorylation is believed to be a critical step in neurofibrillary degeneration in AD, tau protein kinases become obvious therapeutic targets" (p. 403, column 2, bottom) and that since tau phosphorylation appears to be the primary contributor of paired helical filament/neurofibrillary tangle formation and microtuble disruption, inhibition of tau phosphorylation has been proposed as a therapeutic target" (p. 405, paragraph bridging columns 1-2).

Regarding CK1 of SEQ ID NO:1, the teachings of Graves are set forth above.

Regarding tau of SEQ ID NO:2, the teachings of Vitek are set forth above.

Regarding determining the phosphorylation state of a full-length purified tau by mass spectrometry, at the time of the invention, one of ordinary skill in the art would have recognized the use of mass spectrometry as an alternative to immunoassay for analyzing the phosphorylation state of a polypeptide. See, *e.g.,* the references of Hasegawa and Yamamoto, which disclose using mass spectrometry to identify phosphorylated residues of a purified full-length tau polypeptide, including determining the phosphorylation state of S289 (see Hasegawa at p. 17051, Figure 5 and Yamamoto

at p. 257), which is not indicated as being phosphorylated in the results of Hasegawa and Yamamoto. Regarding claim 27, the methods of Hasegawa and Yamamoto involve proteolytically cleaving tau into fragments (see, *e.g.,* Hasegawa at p. 17048, column 1 and Yamamoto at p. 256, column 2). Regarding claim 36, the term "substrate" has been interpreted as encompassing a phosphorylatable residue of tau and claim 36 encompasses determining the phosphorylation state of more than one of the phosphorylation sites recited in claim 22.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Anderton, Lau, Graves, Vitek, Hasegawa and Yamamoto to practice the method of Anderton using CK1 and compare the CK1-phosphorylated tau in the presence and absence of a candidate inhibitor using mass spectroscopy according to Hasegawa and Yamamoto. Although the prior art does not appear to expressly teach phosphorylation of S289 of tau by CK1, by comparing the CK1 phosphorylated tau in the presence and absence of a candidate inhibitor using mass spectroscopy, one would have practiced determining whether or not a candidate substance inhibits CK1 phosphorylation of tau at residue S289. One would have been motivated to use CK1 as a tau kinase in the method of Anderton because of the teachings of Lau as set forth above. One would have been motivated to compare tau phosphorylation in the presence and absence of a candidate inhibitor by mass spectroscopy because, as shown by Hasegawa and Yamamoto, this method is comprehensive, *i.e.,* determines phosphorylation of residues of the full length of tau, and does not require an antibody for each particular phosphorylation site of tau. One

would have had a reasonable expectation of success to Anderton, Lau, Graves, Vitek, Hasegawa and Yamamoto to practice the method of Anderton using CK1 and compare tau phosphorylation in the presence and absence of a candidate inhibitor by mass spectroscopy because of the results of Anderton, Lau, Graves, Vitek, Hasegawa, and Yamamoto. Therefore, the method of claims 22, 26-27, 32, 36, 38-39, and 55 would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO REMARKS: To the extent applicant's remarks address the newly applied rejection, the remarks are addressed below. Beginning at p. 13 of the instant remarks, applicant argues a *prima facie* case of obviousness has not been established because amended claim 22 specifically identifies a select number of tau phosphorylation sites rather than any tau phosphorylation site(s), which sites were previously unknown.

Applicant's argument is not found persuasive. As noted above, although the prior art does not appear to expressly teach phosphorylation of S289 of tau by CK1, the methods of Hasegawa and Yamamoto analyze the phosphorylation of a peptide fragment comprising S289 (see Hasegawa at p. 17051, Figure 5 and Yamamoto at p. 256, column 2) and the results show that S289 is not phosphorylated. As such, by comparing tau phosphorylation in the presence and absence of a candidate inhibitor by mass spectroscopy according to the methods of Hasegawa and Yamamoto, one would have necessarily practiced determining whether a candidate substance inhibits CK1 phosphorylation of tau at residues including S289.

[16] Claim(s) 27 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Anderton, Singh1, Singh2, Graves, Vitek, and Litersky as applied to claims 22, 26, 32, 36, 38-39, and 55 above and further in view of Hasegawa.

The teachings of Anderton, Singh1, Singh2, Graves, Vitek, and Litersky as applied to claims as applied to claims 22, 26, 32, 36, 38-39, and 55 are set forth above.

The combination of references does not appear to teach or suggest using a fragment of tau.

Hasegawa teaches that normal tau and PHF-tau isolated from human brain is post-translationally modified to begin with an alanine, not a methionine (p. 17054, column 1; p. 17053, Table I, A19).

At the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Anderton, Singh1, Singh2, Graves, Vitek, Litersky, and Hasegawa to use tau of SEQ ID NO:2 with a deletion of the N-terminal methionine. One would have been motivated to do this because of the teachings of Hasegawa that tau and PHF-tau are modified in the brain to remove an N-terminal methionine. One would have had a reasonable expectation of success to use express tau of SEQ ID NO:2 with the N-terminal methionine removed because of the results of Anderton, Singh1, Singh2, Graves, Vitek, Litersky, and Hasegawa. Therefore, the method of claim 27 would have been obvious to one of ordinary skill in the art at the time of the invention.

[17] Claim(s) 41-42 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Anderton, Singh1, Singh2, Graves, Vitek, and Litersky as applied to claims 22, 26, 32, 36, 38-39, and 55 above OR Anderton, Lau, Graves, Vitek, Hasegawa and Yamamoto as applied to claims 22, 26-27, 32, 36, 38-39, and 55 above and further in view of Zhu.

The teachings of Anderton, Singh1, Singh2, Graves, Vitek, and Litersky as applied to claims as applied to claims 22, 26, 32, 36, 38-39, and 55 are set forth above.

The teachings of Anderton, Lau, Graves, Vitek, Hasegawa and Yamamoto as applied to claims 22, 26-27, 32, 36, 38-39, and 55 are set forth above.

Anderton further teaches the screening assay can be carried out on a large scale using microtitre plates and automated apparatus (column 7, lines 54-56). Anderton does not expressly teach immobilizing a plurality of substrates.

Zhu teaches “In the past, studies of protein activities have focused on studying a single protein at a time, which is often time-consuming and expensive" (p. 40, abstract). Zhu teaches the use of protein chips for protein kinase assay by, *e.g.,* attaching a substrate to a microwell plate and assaying kinase activity (p. 42, paragraph bridging columns 1-2 and p. 43, Figure 2). According to Zhu, “Coupled with mass-spectrometric identification, protein chips might also have wide application in drug discovery…Proteins and small-molecule ligands can be bound to proteins immobilized on a protein chip and the bound molecules identified using…mass spectroscopy" (p. 43, column 1, bottom).

At the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Anderton, Singh1, Singh2, Graves, Vitek, Litersky, and Zhu OR the teachings of OR Anderton, Lau, Graves, Vitek, Hasegawa, Yamamoto, and Zhu to use a protein chip in an inhibitor screening method with tau protein as substrate. One would have been motivated to do this because of the teachings of Anderton and Zhu as set forth above. One would have had a reasonable expectation of success to combine the teachings of Anderton, Singh1, Singh2, Graves, Vitek, Litersky, and Zhu OR the teachings of Anderton, Lau, Graves, Vitek, Hasegawa, Yamamoto, and Zhu to use a protein chip and mass spectroscopy in an inhibitor screening method with tau protein as substrate because of the results of Anderton, Singh1, Singh2, Graves, Vitek, Litersky, and Zhu OR Anderton, Lau, Graves, Vitek, Hasegawa, Yamamoto, and Zhu. Therefore, the method of claims 41-42 would have been obvious to one of ordinary skill in the art at the time of the invention.

Claim Rejections – Double Patenting

[18] The rejection of claims 22, 26, 32, 36, 38-39, and 55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-9 and 12 of US Patent 5,994,084 (same as the reference of Anderton) in view of the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, Graves, Vitek, Hasegawa, Curran, Hanger, and Morishima and the rejection of claims 41-42 further in view of Zhu are withdrawn, not in view of applicant's arguments, but solely in favor of the new rejection under 35 U.S.C. 103(a) set forth below.

[19] Claims 22, 26-27, 32, 36, 38-39, and 55 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of US Patent 5,994,084 (hereafter "'084 patent"; same as the reference of Anderton) in view of the teachings of Singh et al. (*FEBS Lett.* 358:267-272, 1995; cited in the IDS filed on 6/1/06; hereafter "Singh3"), Graves, Vitek, Hasegawa and Yamamoto. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 6 of the '084 patent is drawn to a method of testing a potential therapeutic agent using target cells in vitro, comprising; 1) providing a cell as claimed in claim 1, said cell exhibiting hyperphosphorylation of the protein tau, 2) incubating said potential therapeutic agent with said cell, and 3) subsequently measuring the extent to which said protein tau is phosphorylated, wherein a reduction in phosphorylation relative to that observed in a cell of claim 1 not incubated with said potential therapeutic agent indicates that said agent is a potential therapeutic. The cell of claim 1 of the '084 patent is a cell recombinantly expressing a tau and GSK-3α or GSK-3β.

The differences between claim 6 of the '084 patent and the claims of this application are: the '084 patent does recite using a combination of GSK-3β and CK1 as a tau-phosphorylating kinase; does not recite CK1 of SEQ ID NO:1; does not recite tau of SEQ ID NO:2; and does not recite determining the phosphorylation state of a full-length purified tau, which includes S289, by mass spectrometry.

Regarding using a combination of GSK-3α or GSK-3β and CK1 as a tau-phosphorylating kinase, the reference of Singh3 teaches that prephosphorylation of tau by CK1 stimulated phosphorylation of tau by GSK-3 as compared to tau that was not prephosphorylated and allows GSK-3 to rapidly phosphorylated some of the same epitopes seen in PHF-tau (p. 271, column 1, bottom).

Regarding CK1 of SEQ ID NO:1, the teachings of Graves are set forth above.

Regarding tau of SEQ ID NO:2, the teachings of Vitek are set forth above.

Regarding determining the phosphorylation state of a full-length purified tau by mass spectrometry, the teachings of Hasegawa and Yamamoto are set forth above.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify claim 6 of the '084 patent to use a combination of GSK-3α or GSK-3β and CK1; to use the CK1 of Graves and the tau of Vitek; and to determine the phosphorylation state of tau by mass spectrometry according to the method of Hasegawa and Yamamoto. One would have been motivated to use a combination of GSK-3α or GSK-3β and CK1 as a tau kinase in the method of claim 6 because of the teachings of Singh3 as set forth above. One would have been motivated to use the CK1 of Graves and the tau of Vitek because these are disclosed in the prior art as being CK1

and tau encoding sequences. One would have been motivated to compare tau phosphorylation in the presence and absence of a candidate inhibitor by mass spectroscopy because, as shown by Hasegawa and Yamamoto, this method is comprehensive, *i.e.,* determines phosphorylation of residues of the full length of tau, and does not require an antibody for each particular phosphorylation site of tau. One would have had a reasonable expectation of success to modify claim 6 of the '084 patent to use a combination of GSK-3α or GSK-3β and CK1; to use the CK1 of Graves and the tau of Vitek; and to determine the phosphorylation state of tau by mass spectrometry according to the method of Hasegawa and Yamamoto because of the results of Singh3, Graves, Vitek, Hasegawa, and Yamamoto.

[20] Claims 41-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 of US Patent 5,994,084 in view of the teachings of Singh3, Graves, Vitek, Hasegawa, and Yamamoto as applied to claims 22, 26-27, 32, 36, 38-39, and 55 and further in view of Zhu. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The teachings of Singh3, Graves, Vitek, Hasegawa, and Yamamoto as applied to claims 22, 26-27, 32, 36, 38-39, and 55 are set forth above.

The teachings of Zhu as applied to claims 41-42 are set forth above.

At the time of the invention, it would have been obvious to use a protein chip as taught by Zhu in the method of claim 6 of the '084 patent. One would have been motivated to do this in view of the advantages as taught by Zhu. One would have had a reasonable expectation of success to use a protein chip as taught by Zhu in the method of claim 6 of the '084 patent because of the results of Singh3, Graves, Vitek, Hasegawa, Yamamoto, and Zhu.

RESPONSE TO REMARKS: To the extent applicant's remarks address the newly applied rejection, the remarks are addressed below. Beginning at p. 15 of the instant remarks, applicant argues a *prima facie* case of obviousness has not been established because amended claim 22 specifically identifies a select number of tau phosphorylation sites rather than any tau phosphorylation site(s), which sites were previously unknown.

Applicant's argument is not found persuasive. As noted above, although the prior art does not appear to expressly teach phosphorylation of S289 of tau by CK1, the methods of Hasegawa and Yamamoto analyze the phosphorylation of a peptide fragment comprising S289 (see Hasegawa at p. 17051, Figure 5 and Yamamoto at p. 256, column 2) and the results show that S289 is not phosphorylated. As such, by comparing tau phosphorylation in the presence and absence of a candidate inhibitor by

mass spectroscopy according to the methods of Hasegawa and Yamamoto, one would have necessarily practiced determining whether a candidate substance inhibits CK1 phosphorylation of tau at residues including S289.

Conclusion

[21] Status of the claims:

- Claims 22, 26-27, 31-36, 38-46, and 53-55 are pending.
- Claims 31, 33-35, 40, 43-46, and 53-54 are withdrawn from consideration.
- Claims 22, 26-27, 32, 36, 38-39, 41-42, and 55 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
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